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ORIGINAL INVESTIGATION

Differential modulation of emotion processing brain regions by noradrenergic and serotonergic antidepressants

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Abstract
Rationale Most widely used antidepressant drugs affect the serotonergic and noradrenergic pathways. However, there are currently no neurobiological criteria for selecting between these targets and predicting the treatment response in individual depressed patients.
Objectives The current study is aimed at differentiating brain regions known to be pathophysiologically and functionally involved in depression-related emotion processing with respect to their susceptibility to serotonergic and noradrenergic modulation.
Methods In a single-blind pseudo-randomized crossover study, 16 healthy subjects (out of 21 enrolled) were included in analysis after ingesting a single dose of citalopram (a selective serotonin-reuptake inhibitor, 40 mg), reboxetine (a selective noradrenaline-reuptake inhibitor, 8 mg), or placebo at three time points prior to functional magnetic resonance imaging (fMRI). During fMRI, subjects anticipated and subsequently viewed emotional pictures. Effects of serotonergic and noradrenergic modulation versus placebo on brain activity during the perception of negative pictures were analyzed with a repeated measures ANOVA in the whole brain and in specific regions of interest relevant to depression.
Results Noradrenergic modulation by reboxetine increased brain activity in the thalamus, right dorsolateral prefrontal cortex and occipital regions during the perception of negative emotional stimuli. Citalopram primarily affected the ventrolateral prefrontal cortical regions.
Conclusion The brain regions involved in the processing of negative emotional stimuli were differentially modulated by selective noradrenergic and serotonergic drugs: thalamic activity was increased by reboxetine, whereas citalopram primarily affected ventrolateral prefrontal regions. Thus, dysfunction in these regions, which could be identified in depressed patients, may predict treatment responses to either noradrenergic or serotonergic antidepressants.

Keywords Citalopram · Reboxetine · Depression · Emotion processing · Functional neuroimaging

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Introduction

Selecting the optimal antidepressant drug to achieve a good clinical response in an individual depressed patient remains a challenge in psychiatric praxis. Currently, there are no validated neurobiological treatment-selection criteria that dictate which type of antidepressant to use (Mayberg 2003; Bruder et al. 2008), and many patients exhibit considerable treatment resistance in depression. In the future, it may be possible to obtain brain activation patterns in individual patients using functional neuroimaging to provide a basis

for selecting the most efficient drug more quickly and reliably.

An important step towards such a strategy would be identifying which brain regions that are altered in depression and involved in emotion processing-related activity are susceptible to antidepressant agents. With this knowledge, one could identify regions with dysfunctional or pathophysiologically relevant information processing in a single depressed patient and then prescribe an antidepressant compound that can modify the information processing to promote mental health.

Functional neuroimaging studies in depression have repeatedly shown increased brain activity in response to particularly emotionally negative stimuli (pictures and faces) in a network of regions comprising the amygdala, ventral or pallidostriatum, thalamus, hippocampus, ventral and dorsolateral prefrontal cortex (VLPFC, DLPFC), insula, ventral and subgenual regions of the anterior cingulate cortex, and occipital visual regions (Elliott et al. 2002; Kumari et al. 2003; Phillips et al. 2003; Herwig et al. 2010).

During the course of treatment, brain activity can change or "normalize" in these regions (Sheline et al. 2001; Davidson et al. 2003; Fu et al. 2004; Little et al. 2005; Keedwell et al. 2009; Frodl et al. 2011; meta-analysis—Fitzgerald et al. 2008). Thus, applying clinically effective treatments can influence brain activity in previously "dysfunctional" regions, corresponding to the clinical improvement.

Currently available antidepressant drugs primarily act on monoaminergic pathways, especially the serotonergic and/or the noradrenergic systems (Schloss and Henn 2004). In the current study, we used functional magnetic resonance imaging (fMRI) to examine the responses of healthy subjects exposed to emotionally relevant stimuli after an acute serotonergic and noradrenergic challenge in a single-blind placebo-controlled crossover design. Single doses of either citalopram, the most selective serotonin-reuptake inhibitor (Hyttel 1982), or reboxetine, the most selective noradrenaline reuptake inhibitor (Tatsumi et al. 1997), were expected to enhance serotonergic or noradrenergic transmission in those regions (1) activated by the task and (2) modulated by serotonergic or noradrenergic neurons. During the task, subjects were presented negative, positive, and neutral emotional pictures after a cued anticipatory period. An analysis of the anticipation period has been reported previously (Brühl et al. 2010). Here, we focused on the perception of negative pictures because this type of stimuli has revealed clear differences in brain activity in depressed patients (Sheline et al. 2001; Elliott et al. 2002; Kumari et al. 2003; Fu et al. 2004; Fitzgerald et al. 2008).

We hypothesized that the two antidepressants tested would exhibit distinct modulating influences on emotion processing in the aforementioned network of brain regions. The resulting distinguishable patterns of modulated brain regions may serve as future target regions for treatment prediction purposes. We analyzed pharmacological effects in the whole brain and in anatomically defined regions of interest (ROIs) in the amygdala, anterior insula, thalamus, DLPFC, and anterior cingulate cortex.

Materials and methods

Subjects

Twenty-one healthy subjects (mean age 28.1 years, right-handed, 14 females) were recruited. After receiving a complete description of the study, they gave written informed consent. The study was approved by the local ethics committee. Subjects did not have any current or previous neurological or psychiatric illnesses, as assessed by a semi-structured interview. Additional exclusion criteria included pregnancy; current medications (except for oral contraceptives); excessive consumption of alcohol, cigarettes, and caffeine; and contraindications against MRI examination. Prior to inclusion, subjects completed a self-rating assessment of depression and anxiety (for demographic and psychometric data, see Online Resource 1). Each of the subjects was intended to undergo three scans. However, a total of five subjects were excluded from analysis due to pathological findings (one subject), withdrawal from the study (one subject), or excessive head movements throughout scanning (three subjects). One scan from each of three of the remaining 16 subjects (mean age 28.4 years, 12 females) could not be completed due to technical problems during scanning. In total, we obtained 45 datasets that were included in the analysis (outlined graphically in Online Resource 2).

Drug treatment

Prior to each scan, each subject received a typical therapeutic dose of citalopram (CIT, 40 mg), reboxetine (RBX, 8 mg), or placebo (PLC, lactose) in a pseudo-randomized order. The tablets were dispensed in a sealed, neutral wrapping such that subjects were unaware of which drug they were taking. Subjects were instructed to take the respective tablets about 2.5 h prior to scanning because peak concentrations of both drugs are observed 2–4 h after oral application (Fleishaker 2000; Joubert et al. 2000). At this therapeutic dose of citalopram, serotonin-transporter occupancy exceeds 80% (Meyer et al. 2004). Similar data for occupancy of the noradrenaline transporter after reboxetine treatment are currently unavailable. A minimal washout period of 1 week was implemented between each

scan, corresponding to at least five half-lives of each substance. The order of drug administration across sessions was counterbalanced by pseudo-randomization. Before and after scanning, subjects were asked about any perceived side effects and their experiences with the experiment in the scanner.

Experimental design

During fMRI scanning, participants performed a task (programmed with Presentation™, Neurobehavioral Systems, USA) comprising 56 trials with expectation and perception of emotional pictures (detailed description in Herwig et al. 2007). Within each trial, a cue was given (duration 1,000 ms), depicting either a "smiling" ("positive") "∪", "non-smiling" ("negative") "∩", or "neutral" symbol "–" that indicated the emotional valence of the upcoming picture, or an "unknown" symbol "|", after which either a pleasant or an unpleasant picture appeared randomly. Thereafter, the respective emotional picture was presented. Notably, the term "unknown" as used here refers to the fact that the emotional valence of the upcoming picture was unknown because it was cued ambiguously. The cues were 1/20th the height of the screen, and the pictures filled the screen. This cueing design was chosen, among other reasons, to reduce anticipatory and preparatory activation caused by the emotional pictures. The "unknown" condition was intended only for the anticipatory phase; the respective pictures were not analyzed.

The anticipation period lasted 6,920 ms [fixation point; cue plus anticipation=4 repetition times of MRI scanning (TR)]. Subsequently, emotional pictures from the International Affective Picture System (IAPS) were presented for 7,920 ms (4 TR). The following baseline period (15,840 ms, 8 TR) was of sufficient duration to allow the blood oxygen level-dependent signal to wear off before the next trial. Each condition consisted of 14 trials in a randomized order.

Participants were instructed to expect emotional stimuli following the cue, to be aware of the indicated emotional valence, and to look at the upcoming emotional picture.

Before scanning, all participants performed a training session, during which they were presented a shorter version of the task with similar pictures. To avoid memory effects, the pictures from the training session did not appear during the main task. Thus, the participants were familiar with the timing, cues, and range of content of the pictures. Three sets of 56 stimuli each were randomly assigned to the sessions. Within and between these sets, stimuli were matched with respect to valence, complexity, and content (IAPS picture rating; for detailed information, see Brühl et al. 2010).

Immediately after each scan, subjects rated the emotional valence of the presented pictures (presented again as printouts) on a nine-point rating scale (1—very negative/unpleasant, 9—very positive/pleasant).

FMRI acquisition

Imaging was performed using a 3.0-T GE Signa HD Scanner (GE Medical Systems, USA, eight-channel head coil). Echo-planar imaging (EPI) was performed for fMRI [repetition time (TR)/echo time (TE) 1,980 ms/32 ms, 22 sequential axial slices, whole brain, slice thickness/gap 4.5 mm/0.5 mm, voxel size 3.4 mm×3.4 mm×5 mm, matrix 64 pixels×64 pixels, field of view 220 mm]. Altogether, 908 volumes within one run were obtained per session. High-resolution 3-D T1-weighted anatomical volumes were acquired (voxel size 1 mm×1 mm×1 mm, axial orientation) for co-registration with the functional data. Furthermore, T2-weighted images in parallel to the EPI sequence were acquired to exclude possible T2-sensitive abnormalities. Stimuli were presented via digital goggles (Resonance Technologies, USA).

fMRI data analysis and statistics

fMRI data were analyzed using BrainVoyager QX 2.07 (Brain Innovation, The Netherlands). Preprocessing included motion correction, slice scan time correction, high frequency temporal filtering, and removal of linear trends. Functional and 3-D structural measurements were co-registered and structural and functional data sets were transformed into Talairach space, resulting in a voxel size of 3 mm×3 mm×3 mm. Finally, the datasets were spatially smoothed with an 8-mm full-width half-maximum Gaussian kernel for subsequent group analysis.

The design matrix was built for analyzing intra-subject comparisons between the three treatment conditions (CIT, RBX, and PLC). The functional data were convoluted with a two-parameter gamma hemodynamic response function (HRF). There are no direct methodological studies addressing the potential effects of citalopram and reboxetine on HRF. Two studies, however, mentioned no changes of the hemodynamic reaction by reboxetine in a visual (Miskowiak et al. 2007) and citalopram in a motor task (Wingen et al. 2008).

In the first step of our analysis, separate beta maps for each subject were computed for the single contrast "negative">"neutral" (ng>nt) and "positive">"neutral" (ps>nt) for each of the treatment conditions. These maps were then combined in a repeated measures ANOVA with the within-subjects factors "treatment" (CIT, RBX, PLC)

and "condition" (ng>nt, ps>nt). For results of the comparison *between* the two active substances (RBX>CIT), see the Online Resource 4. The statistical significance level was set at p <0.0005, which corresponds to an FDR-corrected level of at least q <0.05. We used a cluster threshold of five voxels of 3 mm×3 mm×3 mm (135 mm^3).

Additionally, we analyzed the influence of citalopram and reboxetine in anatomically defined ROIs by positioning cubic ROIs in the bilateral amygdala, bilateral thalamus, and bilateral rostral and ventral anterior cingulate cortex (edge length 10 mm, resulting volume 1,000 mm^3) as well as the bilateral DLPFC and the bilateral anterior insula (edge length 15 mm, resulting volume 3,375 mm^3). For each ROI, the mean effect sizes were computed based on all voxels included in that particular ROI. We compared mean beta weights using a repeated measures ANOVA and calculated effect sizes (Cohen's d). Anatomical regions were identified according to the Talairach system. The results of the anticipation period have been published previously (Brühl et al. 2010).

Results

Behavioral analysis

Single doses of citalopram and reboxetine had no influence on ratings of the emotional valence of the pictures compared to placebo (see Online Resource 3).

Noradrenergic modulation compared to placebo

Enhanced noradrenergic neurotransmission by reboxetine increased brain activity associated with perceiving negative versus neutral pictures subcortically in the bilateral caudate and the dorsomedial thalamus (Fig. 1a–c), including the pulvinar. Cortically, reboxetine influenced the right superior frontal gyrus, bilateral posterior cingulate and cuneus, and bilateral temporal and occipital regions (Table 1, Fig. 1d, e). There were no significant effects of noradrenergic modulation on the brain activity during the perception of positive versus neutral pictures.

Serotonergic modulation compared to placebo

Pre-treatment with citalopram caused less of a decrease in brain activity than placebo in bilateral basal frontal regions (VLPFC, Fig. 2) and increased brain activity in the right middle temporal and middle occipital gyrus (Table 1) during the perception of negative versus neutral pictures. There were no regions with decreased activity due to citalopram.

Serotonergic modulation had no effects on brain activity associated with perceiving positive versus neutral pictures.

Noradrenergic modulation compared to serotonergic modulation

When comparing the effects of noradrenergic and serotonergic modulation directly, the strong influence of reboxetine on the processing of negative emotional stimuli became more noticeable than in comparison with placebo (see Online Resource 4, Table 4.1). Particularly, the impact on subcortical brain regions was clearly seen in an extended subcortical area including amygdalar, thalamic, midbrain, and striatal regions and ranging from the anterior cingulate to the fusiform gyrus bilaterally. Furthermore, bilateral frontal and parietal regions were noradrenergically modulated. During the perception of negative versus neutral pictures, there were no regions with increased activity due to serotonergic influences.

During the perception of positive versus neutral pictures, the effects of noradrenergic versus serotonergic modulation was weaker (Online Resource 4, Table 4.2) when compared to the effects during the negative condition. Reboxetine increased brain activity in the left superior frontal cortex and in a region extending from the right anterior insula to the claustrum, whereas citalopram increased activity in a small region in the left middle temporal gyrus.

Effects of noradrenergic and serotonergic modulation in selected ROIs during the perception of negative versus neutral pictures

In the bilateral amygdala and the thalamus, reboxetine increased brain activity during the perception of negative versus neutral pictures to a much greater extent than citalopram (Table 2). Citalopram inhibited brain activity in the left thalamus, but PLC did not. The anterior insula was bilaterally modulated by reboxetine but not citalopram. In the right DLPFC, we found a large effect of reboxetine compared to placebo and very large effects of reboxetine in the bilateral DLPFC compared to citalopram, which had no significant effect in the bilateral DLPFC. In the two regions of the anterior cingulate cortex (ACC), the only observed drug effect was a modulating impact of reboxetine in the right ventral ACC when compared to citalopram.

Discussion

The aim of our study was to identify brain regions that are specifically modulated by noradrenergic and serotonergic antidepressants during the processing of negative emotional stimuli. Compared to serotonergic agents and placebo, noradrenergic enhancement had the strongest effects in thalamic and other subcortical areas. In contrast, serotonergic modulation altered brain activity primarily in distinct

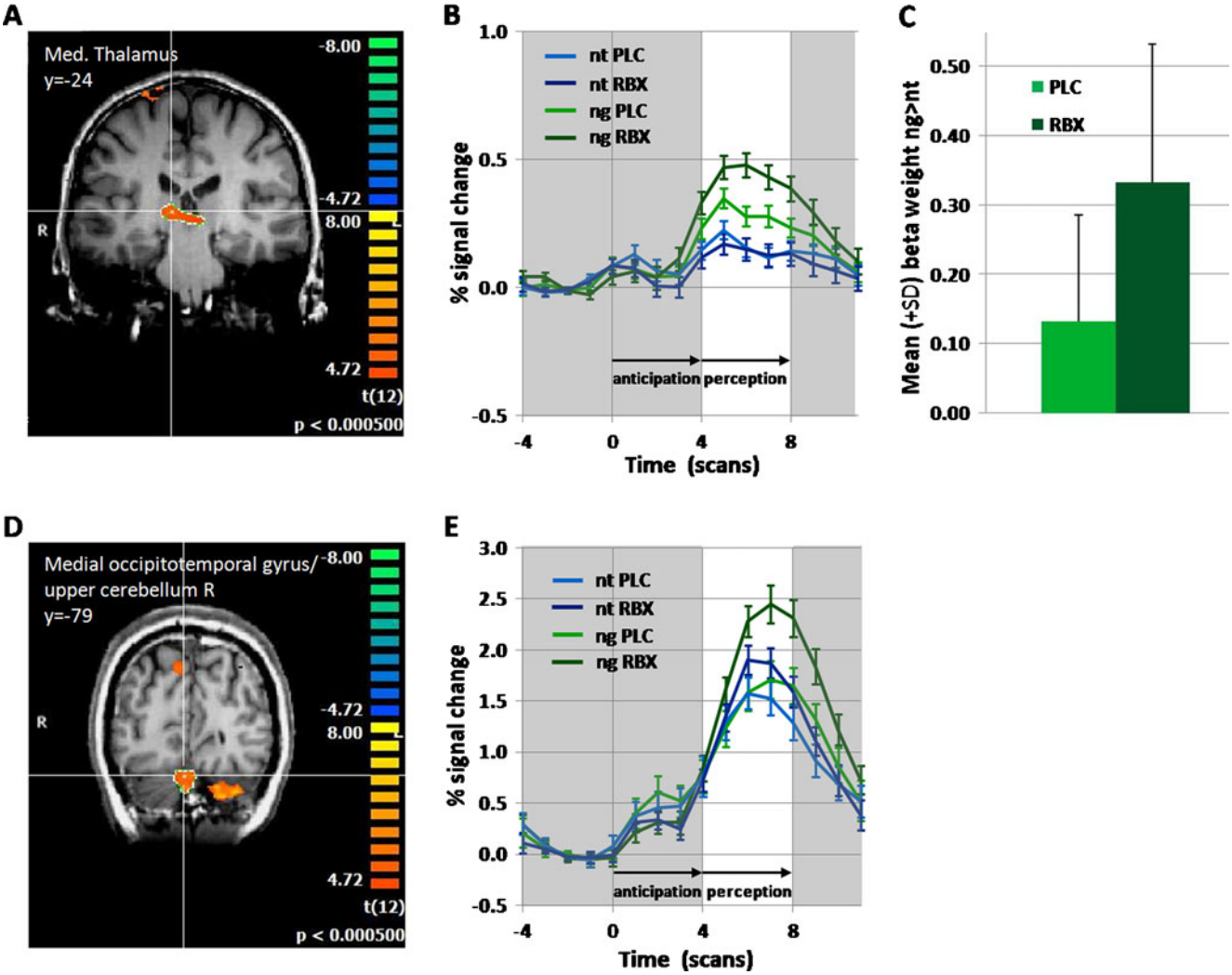

Fig. 1 Modulation of activity in dorsomedial thalamus (**a**, **b**, **c**) and right medial occipitotemporal gyrus (**d**, **e**) by noradrenergic reuptake-inhibition (*RBX*) compared to placebo (*PLC*). In the *left panel*, a coronal brain section with the significant clusters (**a**, **d**), position indicated by the *y*-coordinate. In the *middle panel*, the respective averaged event-related time courses of BOLD response (**b**, **e**) with the perception period in the bright field. The *box plot* on the *right* (**c**) shows the mean beta weights of the conditions reboxetine and placebo in the thalamic cluster. Intra-subject repeated measures ANOVA (n= 13, p<0.0005, *color bars* representing t values). Abbreviations: *R* right, *ng* negative, *nt* neutral

frontal and occipital regions. In the bilateral amygdalar, thalamic, and anterior insular and dorsolateral prefrontal regions, when anatomically defined, noradrenergic enhancement increased brain activity during the processing of negative pictures. In the cingulate cortex, the rostral part was not modulated by the influence of either neurotransmitter system, but the ventral region was sensitive to noradrenergic modulation. During the perception of positive stimuli, influences of noradrenergic enhancement could only be detected in the comparison with the serotonergic modulation in a prefrontal region and in a region extending from the anterior insula to the claustrum, whereas in the same comparison citalopram affected one area in the middle temporal lobe.

The brain regions modulated here during the perception of negative emotional stimuli are sites of action for selective reuptake-inhibiting antidepressants (Cipriani et al. 2009). The behavioral improvements observed after antidepressant treatment may depend upon adaptive and neuroplastic changes that occur in regions expressing neurotransmitter transporters after repeated administration of antidepressant drugs (Katz et al. 2004; Donnici et al. 2008). The advantage of the current approach over simply mapping the binding sites of the respective antidepressants, which has been done previously (e.g., Laruelle et al. 1988; Varnas et al. 2004; Schou et al. 2005), is that the current approach provides information about the interaction of pharmacological and task-induced changes of brain activity

Table 1 Brain regions with increased activity after pre-treatment with citalopram and reboxetine compared to placebo during the perception of negative versus neutral emotional pictures

	Brodmann area	Tal *x*, *y*, *z*	Cluster size (mm^3)	*t* max	*p* max
Reboxetine>placebo					
Superior frontal gyrus/DLPFC R	6	19, −17, 71	1,141	12.02	0.000000
Posterior cingulate R	23	9, −22, 22	287	5.49	0.000138
Posterior cingulate L	23	−6, −25, 25	138	5.54	0.000128
Posterior insula L	13	−30, −34, 13	295	5.89	0.000074
Superior temporal gyrus L	22	−66, −4, 6	384	−8.77	0.000001
Middle temporal gyrus R	20	63, −43, −14	259	8.22	0.000003
Fusiform gyrus L	37	−51, −58, −23	555	7.95	0.000004
Inferior occipital gyrus R	18	42, −88, 1	240	10.47	0.000000
Inferior occipital gyrus L	18	−39, −97, −2	484	9.39	0.000001
Cuneus R	19	21, −95, 28	197	7.86	0.000004
Precuneus R	19	6, −76, 37	1,716	6.84	0.000018
Medial occipitotemporal gyrus/upper cerebellum R (Fig. 1d)		3, −76, −37	1,060	8.78	0.000001
Anterior thalamus/caudate head R		3, 0, 16	1,747	11.33	0.000000
Caudate head L		−6, 17, 4	414	10.44	0.000000
Thalamus/pulvinar R (Fig. 1a)		12, −28, 7	2,902	7.70	0.000006
Cerebellum L		−33, −76, −35	560	7.31	0.000009
Citalopram>placebo					
Inferior frontal gyrus/VLPFC R (Fig. 2)	10	42, 44, −2	387	6.14	0.000026
Inferior frontal gyrus/VLPFC R	46	55, 38, 10	616	9.77	0.000000
Middle temporal gyrus R	21	63, −61, 10	1,359	7.71	0.000002
Middle occipital gyrus R	19	24, −100, 14	391	8.21	0.000001

Given are Talairach coordinates of the peak activation of the cluster and the cluster size in cubic millimeters ($p<0.0005$, corresponding to $q<0.05$ FDR-corrected, extent-threshold 135 mm^3 contiguously)

L left, *R* right, *D/VLPFC* dorso-/ventrolateral prefrontal cortex

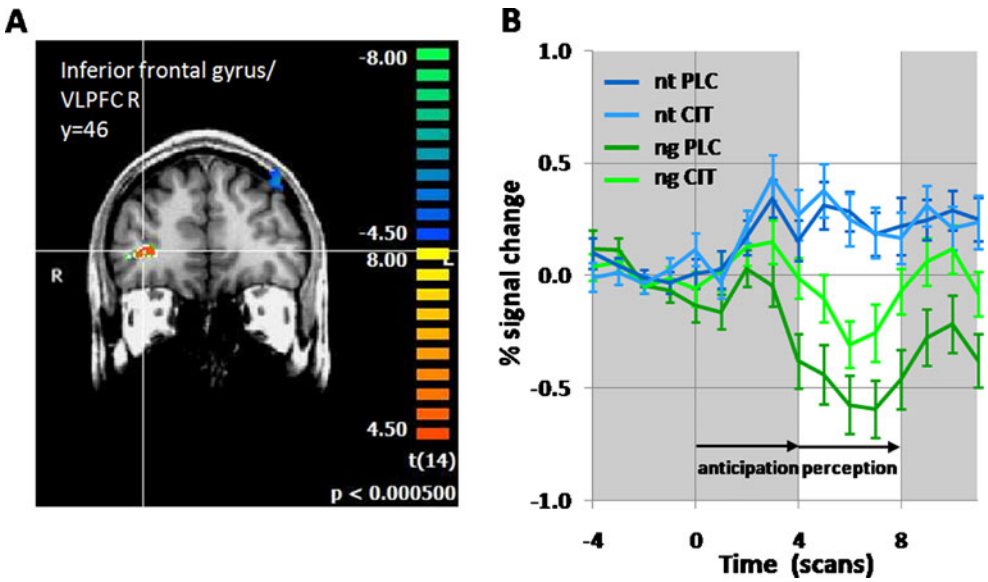

Fig. 2 Serotonergic modulation of activation in the right inferior frontal gyrus/ventrolateral prefrontal cortex (VLPFC) by citalopram (*CIT*) compared to placebo (*PLC*). On the *left panel*, a coronal brain section with the significant cluster (**a**), position indicated by the *y*-coordinate. In the *right panel*, the respective averaged event-related time course of BOLD response (**b**) with the perception period in the bright field. Intra-subject repeated measures ANOVA ($n=15$, $p<0.0005$, *color bars* representing *t* values). Abbreviations: *R* right, *ng* negative, *nt* neutral

Table 2 Effects of citalopram and reboxetine in anatomically defined regions of interest (ROIs)

Anatomic region	Tal	CIT>PLC		RBX>PLC		RBX>CIT	
	x, *y*, *z*	*t*/*p*	*d*	*t*/*p*	*d*	*t*/*p*	*d*
Amygdala R	20, −7, −15	0.234/0.812	0.08	1.629/0.129	0.57	**2.552/0.025**	*0.89*
Amygdala L	−20, −7, −15	0.270/0.791	0.08	1.452/0.172	0.09	**2.672/0.019**	*0.76*
Thalamus R	9, −14, 6	−1.562/0.141	0.46	1.556/0.146	0.69	**3.769/0.002**	**1.38**
Thalamus L	−9, −14, 6	**−2.518/0.025**	0.65	*1.945/0.076*	*0.93*	**4.216/0.001**	**1.49**
Anterior insula R	33, 13, 4	−0.538/0.599	0.19	0.209/0.838	0.09	*2.111/0.055*	*0.88*
Anterior insula L	−33, 13, 4	−1.292/0.217	0.47	*1.985/0.070*	0.67	**3.904/0.004**	**1.63**
Rostral anterior cingulate R	6, 29, 9	0.771/0.454	0.21	*1.913/0.080*	*0.82*	*1.951/0.073*	0.66
Rostral anterior cingulate L	−6, 29, 9	1.033/0.319	0.32	0.226/0.825	0.08	1.713/0.110	0.56
Ventral anterior cingulate R	6, 12, 25	0.215/0.806	0.09	0.499/0.627	0.21	**2.691/0.019**	*1.03*
Ventral anterior cingulate L	−6, 12, 25	0.538/0.599	0.18	0.896/0.388	0.39	*1.922/0.077*	0.62
DLPFC R	42, 10, 33	−0.243/0.812	0.08	*2.109/0.057*	*0.77*	**3.449/0.004**	**1.17**
DLPFC L	−42, 10, 33	−1.692/0.113	0.52	1.650/0.125	0.35	**2.896/0.012**	**1.17**

Size of the cubes 1,000 mm^3, except for anterior insula and DLPFC: 3,375 mm^3

R right, *L* left, *DLPFC* dorsolateral prefrontal cortex, *Tal* Talairach coordinates of the centers of cubic ROIs, *t*/*p* paired Student's *t* test (mean beta weights of the ROI, $p<0.05$ in bold, $p<0.10$ in italic), *d* Cohen's *d* of the mean beta weights of the ROI [$d>0.75$ large effect (italic), $d>1.10$ very large effect (bold), $d>1.45$ huge effect (bold)]

in various brain regions during the processing of pathophysiologically relevant emotional stimuli. The modulating effects of the drugs were expected to be dependent on the task-induced activation of various brain regions.

The regions identified as serotonin and noradrenaline responsive in the current study correlate well with previous studies localizing noradrenaline transporters (Schou et al. 2005) and serotonin transporters (Laruelle et al. 1988; Varnas et al. 2004) using autoradiographic and positron emission tomographic methods. However, noradrenaline and serotonin transporters are widespread according to these localizing studies. Therefore, the additional functional approach increases the specificity of the results.

Previous studies examining interactions between behavioral tasks and pharmacological influences on brain activity using pharmaco-fMRI have revealed somewhat divergent results. For example, citalopram has been shown to *increase* amygdala activity in response to facial expressions (Bigos et al. 2008) and without any stimulus (McKie et al. 2005), but it has also been shown to *reduce* amygdala responses to fearful facial expressions (Murphy et al. 2009). Frontal cortex activity has been shown to *increase* after citalopram during the recognition of disgusted faces (Anderson et al. 2007), whereas in a sustained attention task citalopram *decreased* prefrontal activity (Wingen et al. 2008). Thalamic activity was *reduced* in the same study (Wingen et al. 2008). However, during the recognition of disgusted faces, citalopram *increased* thalamus activity (Anderson et al. 2007). Furthermore, temporal, insular, and occipital regions are modulated by citalopram (Anderson et al. 2007; Wingen et al. 2008).

Acute tryptophan depletion (ATD) has been used to reduce availability and levels of serotonin in the brain. Studies applying ATD in healthy subjects during fMRI revealed increased activity in frontal brain regions in response to emotional faces (Fusar-Poli et al. 2007; Daly et al. 2010) as well as during a Stroop task (Horacek et al. 2005), whereas two studies using Go/Nogo paradigms showed decreased activity in frontal regions (Rubia et al. 2005; Evers et al. 2006). Cingulate activity was increased in one study (Fusar-Poli et al. 2007) using emotional faces, but decreased in the other (Daly et al. 2010), whereas insular activity was modulated in the opposite direction during emotional faces (decrease in Fusar-Poli et al. 2007, increase in Daly et al. 2010). Occipital cortical activity was decreased in both studies using emotional faces (Fusar-Poli et al. 2007; Daly et al. 2010).

Studies using reboxetine with emotional and non-emotional tasks showed rather converging results, with reboxetine increasing brain activity in the amygdala, thalamus, putamen, insular, frontal, cingulate, parietal, and occipital regions (Miskowiak et al. 2007; Kukolja et al. 2008; Onur et al. 2009; Grefkes et al. 2010).

Some studies have examined chronic administration of (es)citalopram and reboxetine over the course of 3 to 7 days (or even longer, e.g., Arce et al. 2008; Norbury et al. 2008). Due to the duration of treatment, these results reflect the beginning of chronic antidepressant effects (Katz et al.

2004) in addition to the direct regulatory effects, which are on the intracellular level detectable after 48 h (Donnici et al. 2008), rather than the acute neuromodulatory effects examined in our study.

The noradrenergic and serotonergic systems are involved in different aspects of regulating cognitive-emotional functions. For example, the noradrenergic system is part of the "ascending reticular activating system" and is thus strongly involved in regulating vigilance, alertness, and motivation. In addition to this core involvement, the noradrenergic system also regulates several additional psychological functions, including sensory processing, synaptic plasticity, network tuning, and memory (Sara 2009). The serotonergic system, in contrast, is strongly involved in the regulation of emotional and behavioral control processes (Cools et al. 2008; Martin-Soelch 2010). Decreases in the serotonergic tone of vulnerable subjects have been implicated in depression and anxiety (Cools et al. 2008). Thus, the selective stimulation of one particular system may modulate a particular set of psychological functions.

While there is consistent evidence for a reduced processing of emotionally negative stimuli due to the influence of antidepressants (however particularly with chronic application), the results of previous studies regarding the processing of positive stimuli or the induction of a positive bias are mixed: for example, the acute application of citalopram reduced negative mood, but had only a non-significant effect on positive mood in one study (Harmer et al. 2003), whereas the recognition of positive *and* negative facial expressions was increased. In another study, citalopram and reboxetine increased the N250 amplitude for happy relative to sad facial expression (Kerestes et al. 2009), however without an effect on behavior and mood. Application of citalopram and reboxetine over 7 days resulted in no significant changes of mood in healthy subjects (Harmer et al. 2004) and had no effect on the recognition of happy facial expression, but decreased the recognition of disgusted, angry, and afraid expressions and the emotion-potentiated startle response to negative stimuli, thus pointing to an effect on the processing of negative stimuli. Hence, the weaker effect of noradrenergic and serotonergic modulation in our study is in line with the current findings in this field.

Overall, the results of the current study are in agreement with previous studies using acute modulation of the noradrenergic and serotonergic system. However, our results are the first to demonstrate that noradrenergic and serotonergic antidepressants exhibit differential modulation of brain activity during the perception of emotional stimuli, particularly in subcortical regions such as the thalamus, amygdala and caudate, and also in prefrontal regions. When comparing our current results with our previous analysis of the anticipation period (Brühl et al. 2010), the most prominent difference is the weaker influence of serotonergic modulation in the perceptual phase, as analyzed here. In the previous study, citalopram pre-treatment increased brain activity in prefrontal regions (medial prefrontal cortex, V/DLPFC) during the anticipation of negative and potentially negative stimuli. In the current study, we observed an influence only on the VLPFC activity. Noradrenergic modulation induced an extended, more prominent increase in brain activity during the perception period, with an overlap in the DLPFC, the posterior cingulate, the left superior temporal gyrus, and the thalamic area. Additionally, reboxetine modulated visual-perceptive and higher order visual processing areas, such as the occipital cortex and the (pre)cuneus during the perception of negative stimuli. In the direct comparison between reboxetine and citalopram, we found that the medial thalamus, left extended amygdale, and visual-perceptive and higher order visual processing areas (occipital cortex, fusiform gyrus, and precuneus) were modulated by reboxetine during the anticipatory phase, whereas citalopram acted in the prefrontal and insular regions. Here, during the perception of negative emotional stimuli (see Online Resource 4, Table 4.1), noradrenergic influences were dominant in the frontal, parietal, occipital, and extended subcortical areas, including the thalamus, caudate, and amygdala. During the anticipation and perception of negative stimuli, we found a more prominent influence of reboxetine on the medial thalamus compared to citalopram in both studies.

Regarding the specific region that may indicate improved individual responses to either serotonergic or noradrenergic antidepressant drugs, we propose that noradrenergic-based interventions should be used as first-order treatments in depressed patients with dysfunctions in thalamic regions during the anticipation and perception of negative emotional stimuli because these regions were strongly modulated by reboxetine in our current and previous studies. On the other hand, by also considering our previous findings during the anticipation period (Brühl et al. 2010), serotonergic intervention would be recommended in patients with prefrontal, right V/DLPFC "hyperactivations", particularly during the anticipation of negative emotional stimuli in depression. In a recent study in depressed patients, the right VLPFC was one of the brain regions differentially modulated treated with citalopram over 6 weeks compared to reboxetine (Wagner et al. 2010), thus confirming the relevance of our findings. A recent meta-analysis (Cipriani et al. 2009) indicated a lower efficacy of reboxetine compared drugs with serotonergic effects. However, a neurobiologically based method as, for instance, the one proposed here could help identify subgroups of patients responding to noradrenergic or other compounds. In such subgroups, substances with lower

efficacy over all patients could have higher potency and response rates (Bschor 2010).

Regarding potential modes of action, antidepressants may induce non-specific increases in brain activity in regions that exhibit dysfunctionally increased activity related to depression. Although this may appear counterintuitive at first, increasing non-specific activity in a certain region may induce noise and "override" the dysfunctional depression-related activity via synaptic adaptations and neural reorganization. In this case, chronic treatment with antidepressants could eliminate the dysfunctional information processing that may underlie the aberrant emotion processing observed in depression. Antidepressants may further facilitate the regional processing of functional, not pathophysiologically biased information, thus enabling a recalibration and rebalancing of information processing beyond the dysfunctional "depressive" attractor. Over the course of long-term treatment, neuroplastic changes may consolidate therapeutic effects. Of course, further investigation is required to validate this model. Particularly the transferability of the results to emotion processing in depressed patients has to be investigated in further studies. The principles of our approach, however, may provide a basis for personalized treatment based on neurobiological findings in psychiatric disorders in the future.

One limitation of our study is the relatively low number of subjects and scans that were analyzed. Despite this limitation, the statistical power of our study is sufficient to achieve significance as a result of the crossover design with repeated measures. Furthermore, our study purposely abstains from an explicit behavioral control. Any such behavioral measure would have induced preparatory and executive processes. Behavioral control procedures could have caused distractions from the task itself and reduced emotional involvement. Follow-up interviews with the participants confirmed their attention during scanning. Attention was further verified by monitoring individual brain activation in visual areas. The intake of the administered drugs was not verified by observation or plasma levels, but nearly all subjects reported mild, characteristic drug side effects prior to scanning, a result that is consistent with a high level of compliance. In addition, because non-compliance would lead to an underestimation of antidepressant effects, we are confident in the validity of our results. However, because this study was conducted in healthy subjects, future research will be required to demonstrate the transferability of these results to depressed patients.

In conclusion, our data provide evidence for functionally distinguishable effects of noradrenergic and serotonergic antidepressants in distinct brain areas, particularly during the processing of negative emotional stimuli. This investigation may serve as a step towards future studies evaluating whether antidepressant treatment can be improved by selecting specific antidepressant drugs based on differential patterns of brain activity observed in different patients. Given our current results and previous findings, we propose that such candidate regions may include the thalamic region, the dysfunction of which may indicate responsiveness to noradrenergic stimulation, and the ventrolateral prefrontal regions, the dysfunction of which may indicate preferential responses to serotonergic agents.

Competing interests All authors report no competing interests.

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